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Everolimus and Pasireotide for Advanced and Metastatic Hepatocellular Carcinoma

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Abstract

Purpose—Few treatment options are available for patients with advanced or metastatic hepatocellular carcinoma (HCC). Based on preclinical and early clinical efficacy signals and lack of overlapping toxicity, we undertook this multicenter phase II trial to estimate efficacy and safety of everolimus and pasireotide in advanced HCC.

Methods—Patients with advanced HCC not amenable to locoregional therapy and Child-Pugh A cirrhosis received everolimus 7.5 mg PO daily and pasireotide LAR 60 mg IM every 28 days. The primary endpoint was time to progression (TTP), with 26 events needed to evaluate if everolimus + pasireotide improved TTP from 2.8 to 4.4 months, with 80% power and an alpha of 0.05. Secondary endpoints included response as measured by RECIST modified for HCC, treatment-emergent adverse events, and overall survival.

Results—After 24 patients were enrolled, results of a randomized trial showing no benefit of everolimus in HCC were released prompting an unplanned interim analysis that found the conditional probability of rejecting the null hypothesis based on events in those patients was 0.08. Therefore accrual was halted. Patients had a median age of 59 years, 21 (88%) had BCLC stage C cancer, and 11 (46%) metastatic disease. Median TTP was 3.5 months (95% CI 2-5.8) and median survival 6.7 months (95% CI 6-infinity). Best response was stable disease in 10 patients. Grade 3 hyperglycemia occurred in 6 (25%). There were no grade 4 treatment-emergent events.

Conclusion—Despite promising early efficacy signals, we found no benefit for the combination of everolimus and pasireotide in HCC.

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Keywords

hepatocellular carcinoma; drug therapy; everolimus; pasireotide; phase II trial

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer related mortality world-wide.[1] With an incidence that is nearly equivalent to mortality, HCC is a particularly deadly cancer. In part, this reflects the comorbid cirrhosis of HCC patients, but the high mortality rate also reflects the relative ineffectiveness of current treatment options. Sorafenib is the only approved drug therapy for HCC. In patients with advanced or metastatic HCC and compensated cirrhosis, sorafenib offers disease control in approximately 40% of treated patients, with time to progression of 5.5 months and median survival of 10.7 months, approximately 3 months longer than that of placebo treated patients.[2] New therapies for patients with advanced HCC are desperately needed.

Everolimus is a highly selective inhibitor of the mammalian target of rapamycin (mTOR) that exerts anticancer effect by directly inhibiting tumor cell growth and proliferation as well as by inhibiting angiogenesis via reduction in tumor HIF-1 activity, vascular endothelial growth factor (VEGF) production, and VEGF-induced proliferation of endothelial cells[3]. mTOR signaling is upregulated in a large portion of HCC cell lines, and inhibition of mTOR with rapamycin and everolimus has shown promising preclinical activity.[4-8] In addition to this robust preclinical rationale, estimates of efficacy of weekly everolimus were very promising in a phase I study in hepatocellular carcinoma in which disease control was seen in 71% of patients.[9]

Somatostatin analogs have shown to have antimitotic activity in both endocrine and non-endocrine tumors. Octreotide, the first and most widely tested analog, showed very promising improvement in survival compared with supportive care in an early randomized trial in patients with advanced HCC.[10] Subsequent trials, however, have reported variable clinical activity, though the balance of evidence suggests octreotide offers little benefit for patients with HCC.[11-17] Variable expression of the 5 different somatostatin receptor subtypes on HCC cells may underlie the conflicting results and limited effect of octreotide.[18-20] Octreotide binds only somatostatin receptor 2 with high affinity but binds with low affinity to receptors 3 and 5. In contrast, the novel somatostatin analog pasireotide (SOM230) binds with high affinity to 4 of the 5 known somatostatin receptors. As such, the failure to reproducibly demonstrate a benefit with approaches using somatostatin analogues to date may reflect an inability to appropriately hit the desired target rather than a failure of the approach in HCC.

Based on the preclinical rationale and lack of overlapping mechanism of action and toxicity of these agents, we undertook this multicenter open-label phase II trial to estimate the efficacy and safety of the combination of everolimus and pasireotide in advanced or metastatic HCC.

Methods

This study was approved by the institutional review board at each of the participating sites and registered with clinicaltrials.gov (NCT01488487). All patients gave written informed consent prior to undergoing any study related procedures or testing.

Patients and Treatment

Patients with advanced or metastatic HCC were eligible if the diagnosis had been confirmed by either histopathology or a radiographic appearance characteristic of HCC (e.g. early arterial enhancement with subsequent venous phase washout) on MRI or multiphase CT. Multiple prior locoregional therapies were permitted provided there had been documented disease progression and the disease was no longer amenable to local approaches.

Despite being the standard first-line therapy for advanced disease, prior systemic therapy including sorafenib was not allowed with the exception of prior sorafenib if it was discontinued for intolerance, not disease progression. All patients were informed the standard-of -care therapeutic alternatives to this trial during the informed consent process. Adequate organ function was required as determined by the following criteria: Child-Pugh score of ≤6; INR≤1.5; bilirubin ≤1.5 times institutional upper limit of normal (IULN); AST or ALT ≤3 times IULN; creatinine ≤1.5 times IULN or creatinine clearance ≥50 mL/min; absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 50 \times 10^9$/L; hemoglobin ≥9 g/dL; Fasting serum cholesterol ≤300 mg/dL and fasting triglycerides ≤2.5 times IULN.

Treatment consisted of pasireotide LAR at 60 mg IM every 28 days and everolimus 7.5 mg PO on a continuous daily basis. The LAR formulation of pasireotide was chosen to optimize ease of use compared with twice daily injections. Everolimus adherence was evaluated by patient diary. Patients were evaluated prior to the start of each 28 day cycle for adverse events. Blood sugar was monitored at least every other day via home glucometer. Toxicity was graded using NCI CTCAE version 4.0. Restaging with MRI or triple-phase CT and alpha fetoprotein (AFP) measurements were undertaken every 8 weeks. Radiographic response was measured by RECIST, modified for HCC in which the target lesions are measured by the dimensions of enhancement on the arterial phase.[21] Treatment was administered continuously until disease progression, unacceptable toxicity, or withdrawal.

Statistical Considerations

The primary endpoint was time to progression (TTP), measured from time of study enrollment until radiographic progression. Secondary endpoints were to describe the rate of treatment-emergent adverse events with the everolimus/pasireotide combination, overall survival from enrollment, and the objective response rate (RR). To evaluate whether the everolimus/pasireotide combination improved TTP from the null of 2.8 to 4.4 months, 26 events would be needed to provide 80% power with a one-sided alpha of 0.05. After everolimus failed to show significant single agent clinical activity in the EVOLVE-1 trial, [22] we conducted an interim analysis in September of 2013 to evaluate the conditional power for demonstrating the hypothesized improvement in TTP at study completion based on then current data. The probability of rejecting the null hypothesis was only 0.08,

therefore accrual was halted. Patients were informed of these results and given the option to continue on treatment if deemed in their best interest by the patient and their treating physician. All chose to remain on treatment. Final analysis was conducted in September of 2014 based on events through July 31st, 2014.

Results

Twenty-four patients were enrolled prior to the decision to terminate the study. Patients had a median age of 59 (range 23 – 87) years with a male and Caucasian predominance. Hepatitis C virus was present as a cause of HCC in 7 (29%) and hepatitis B virus in 2 (8%). Median time from diagnosis of HCC to trial enrollment was 4 months (range <1 – 88 months). Eleven of 24 patients had undergone some prior therapy, 8 having had prior surgical resection, 3 had previously been determined to be intolerant to sorafenib. Patients were predominately BCLC C (21, 88%) but had a low median CLIP score 1.5 (interquartile range 1-3). Eleven (46%) patients had metastatic disease at presentation and 9 (37%) had portal vein involvement.

Treatment was administered for a median of two 28 day cycles (range 1-12, interquartile range 1-4). Only three patients required dose reduction with three treatment delays due to everolimus; none required dose reduction or delay of pasireotide. The most common treatment-emergent adverse event was hyperglycemia in 14 (58%), with 6 patients experiencing grade 3, 5 grade 2, and 3 patients with grade 1 hyperglycemia (Table 2). Alkaline phosphatase (2, 8%) and alanine aminotransferase (2, 8%) elevations were the only other grade 3 adverse events occurring in more than one patient. Six patients experienced a total of 9 serious adverse events, all of which were considered to be possibly or probably related to disease, not drug.

At time of analysis, all patients have been removed from protocol therapy: 15 (63%) for progressive disease; 6 (25%) for adverse events requiring removal per protocol; 1 due to death prior to radiographic evaluation though death was clinically attributed to progressive disease; 2 due to intolerance after 2 and 5 cycles. Median TTP was 3.5 months (95% CI 2-5.8) months and median OS 6.7 months (95% CI 6- infinity) months (Figures 1 and 2). No patient experienced radiographic response according to modified RECIST. Ten of 22 evaluable patients had stable disease as their best response.

Discussion

The combination of everolimus and pasireotide has minimal activity as first line therapy for patients with advanced or metastatic HCC. Four patients were maintained on study without progression after their second per-protocol scan at 4 months, remaining on therapy for 5, 5, 9 and 12 cycles each. These patients were older than the average study participants (median age 69 versus 59) and none of them had viral hepatitis, perhaps suggesting a subgroup in whom future somatostatin or mTOR inhibition might be worthy of study. However, they also had a lower median CLIP score, hence their results may reflect a more indolent biology of disease and slower progression to liver failure rather than clinical benefit from the study therapy.

Our finding of lack of benefit of everolimus and pasireotide is supported by recently results of a large randomized trial comparing everolimus to placebo in patients with HCC who had previously demonstrated disease progression or intolerance on first-line sorafenib.[22] Despite the early signal of clinical benefit for single agent everolimus in the phase I setting, time to progression and overall survival in everolimus-treated patients was equivalent to that of placebo treated patients.

Multiple pathways for which targeted therapies are available are thought to be instrumental in the carcinogenesis, invasion, and/or metastasis of hepatocellular carcinoma.[23] Our understanding of how to apply agents that target relevant pathways in HCC, however, remains nascent. This is not only because of the difficulty of testing multiple agents in patients with cirrhosis, but likely also because of marked molecular tumor heterogeneity.[23] Multiple efforts are currently underway to more thoroughly describe the molecular and genetic characteristics of HCC. Incorporation of on-study biopsies of HCC patients may help advance this field more rapidly. Our study did include collection of correlative blood and tissue samples, however no analysis specific to this study has been conducted given the lack of efficacy of this regimen.

In conclusion, the combination of everolimus and pasireotide is ineffective as first-line therapy for HCC.

Acknowledgments

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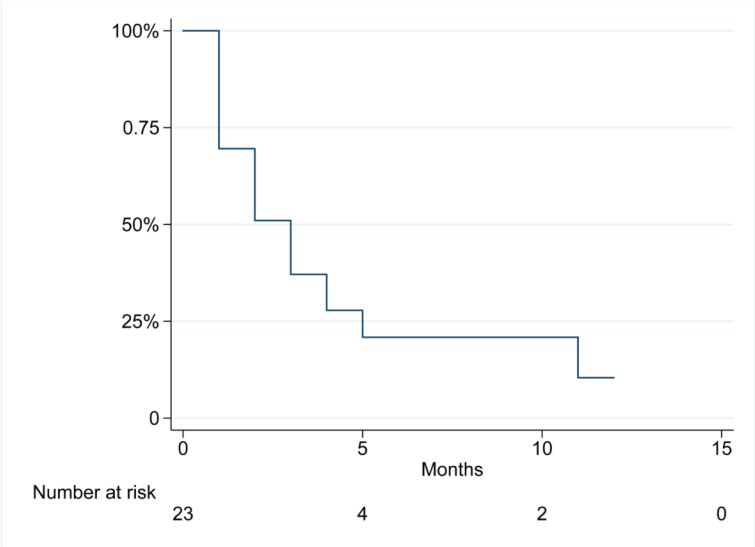

Fig 1. Kaplan-Meier Estimate of Time to Progression

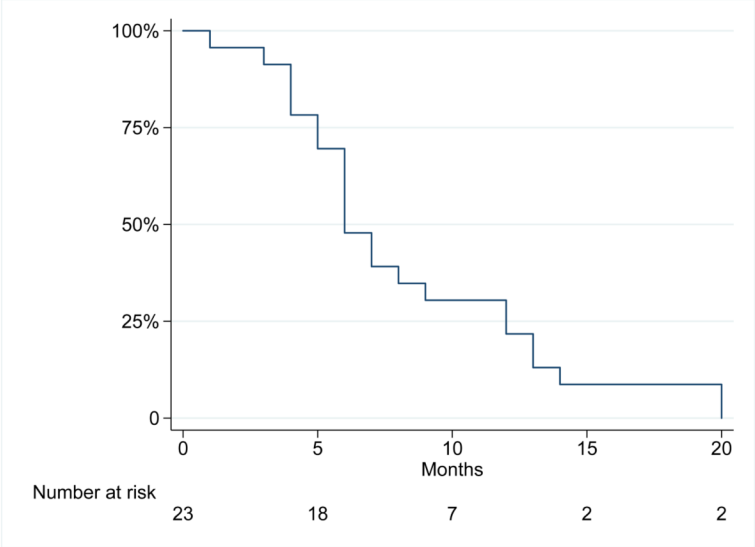

Fig 2. Kaplan-Meier Estimate of Overall Survival

Table 1

Patient Characteristics

Characteristic	All Patients N=24
Age, median (range)	59 (23-87)
Sex, n (%)	
Male	16 (66%)
Female	8 (33%)
Race, n (%)	
White	21 (88%)
Black	1 (4%)
Asian	2 (8%)
Latino, n(%)	0
Chronic Hepatitis C, n (%)	7 (29%)
Chronic Hepatitis B, n (%)	2 (8%)
Child-Pugh Score, median (range)	5(5-6)
Time from Diagnosis to Enrollment, Median months (range)	4(<l-88)
CLIP Score, Median (range)	1.5 (0-5)
BCLC Stage[a], n (%)	
B	2 (8%)
C	21 (88%)
Portal Vein Involvement, n (%)	9 (37%)
Extent of Cancer, n (%)	
Unifocal	2 (8%)
Multifocal	11 (46%)
Metastatic	11 (46%)
Prior Therapy[a], n (%)	
Yes	11 (46%)
No	12 (50%)
Type of Prior Therapy (may have >1)	
TACE	4 (17%)
TARE	2 (8%)
Ablation	2 (8%)
Surgery	8 (33%)

CLIP, Cancer of the Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer.

[a]BCLC is missing for one patient. Prior therapy is missing for one patient.

Table 2
Frequency of Treatment-Emergent Adverse Events

Adverse Event	All Grades N(%)	Grade 1 N(%)	Grade 2 N(%)	Grade 3 N(%)
Hyperglycemia	14 (58%)	3 (13%)	5 (21%)	6 (25%)
Alkaline phosphatase elevation	10 (42%)	4(17%)	4 (17%)	2 (8%)
Mucositis	9 (38%)	6 (25%)	2 (8%)	1 (4%)
Aspartate aminotransferase elevation	9 (38%)	3 (13%)	5 (21%)	1 (4%)
Fatigue	7 (29%)	5 (21%)	2 (8%)	1 (4%)
Alanine aminotransferase elevation	7 (29%)	5 (21%)	0	2 (8%)
Diarrhea	7 (29%)	3 (13%)	3 (13%)	1 (4%)
Rash	6 (25%)	5 (21%)	1 (4%)	0
Thrombocytopenia	5 (21%)	5 (21%)	0	0
Anemia	5 (21%)	4 (17%)	1 (4%)	0
Anorexia	3 (13%)	3 (13%)	0	0
Bilirubin elevation	3 (13%)	1 (4%)	2 (8%)	0
Hypertriglyceridemia	3 (13%)	3 (17%)	0	0
Nausea	3 (13%)	2 (8%)	1 (4%)	0
Neutropenia	3 (13%)	2 (8%)	1 (4%)	0
Elevated cholesterol	2 (8%)	2 (8%)	0	0
Vomiting	2 (8%)	2 (8%)	0	0
Dysgeusia	1 (4%)	1 (4%)	0	0
Edema limbs	1 (4%)	0	1 (4%)	0
Fever	1 (4%)	0	1 (4%)	0
Hypophosphatemia	1 (4%)	0	0	1 (4%)
Lymphopenia	1 (4%)	0	1 (4%)	0
Palmar-plantar erythrodysesthesia	1 (4%)	1 (4%)	0	0
Weight loss	2 (8%)	0	1 (4%)	0
Leukopenia	2 (8%)	2 (8%)	0	0